Volume 9 • Number 1 • 2006
VALUE IN HEALTH

Economic Evaluation of Voriconazole versus Conventional Amphotericin B in the Treatment of Invasive Aspergillosis in Germany

Jeroen P. Jansen, PhD,[1] Winfried V. Kern, MD,[2] Oliver A. Cornely, MD,[3] Meinolf Karthaus, MD,[4] Markus Ruhnke, MD,[5] Andrew J. Ullmann, MD, MPH,[6] Ansgar Resch, MD, MPH[7]

[1]Mapi Values, Houten, The Netherlands; [2]Division of Infectious Diseases, Department of Medicine, University Hospital, Freiburg, Germany; [3]1st Department of Internal Medicine, University of Cologne, Cologne, Germany; [4]Medizinische Klinik II, Evangelisches Johannes-Krankenhaus, Bielefeld, Germany; [5]Department of Medicine II, Charité University Medicine, Campus Charité Mitte, Berlin, Germany; [6]3rd Medical Department, Pfizer Pharma GmbH, Karlsruhe, Germany; [7]Outcomes Research, Pfizer Pharma GmbH, Karlsruhe, Germany

ABSTRACT

Objective: To assess the costs and cost-effectiveness of voriconazole in comparison to conventional amphotericin B (CAB) for the treatment of invasive aspergillosis in Germany.
Methods: The cost-effectiveness of voriconazole in comparison to CAB was evaluated with a lifetime Markov model, focusing on the long-term survival of patients treated for invasive aspergillosis. Long-term survival was extrapolated from survival after 12 weeks of treatment, obtained from a randomized aspergillosis study. Information on medical resource consumption and treatment pathways were obtained from this study and an expert committee. With probabilistic analysis the cost-effectiveness of voriconazole compared with amphotericin B was analyzed and expressed in incremental costs per life-weeks gained. The evaluation was performed from a limited societal perspective (both inpatient and outpatient costs) and hospital perspective (only inpatient costs).
Results: Average survival of patients treated with voriconazole was 174.4 life-weeks (95% confidence interval [CI] 159.4–191.3), compared with 119.4 life-weeks (95% CI 106.4–132.3) for amphotericin B. With voriconazole, the mean total costs per patient were €30,026 (95% CI €23,118–37,947) compared with €26,669 for amphotericin B (95% CI €21,259–34,263) from the limited societal perspective. The corresponding incremental cost-effectiveness ratio was €62 per life-week gained (i.e., €3224 per life-year gained). Hospital costs were approximately 90% of the mean total costs.
Conclusions: In the treatment of invasive aspergillosis, voriconazole is cost-effective in comparison to amphotericin B. Hospital costs are comparable for both treatments and are expected to be reimbursed based on the German diagnosis-related groups (DRG) system 2005.
Keywords: cost-effectiveness analysis, diagnosis-related groups, invasive aspergillosis, reimbursement.

Introduction

Invasive fungal infections are an increasingly important cause of morbidity and mortality particularly in patients with hematologic malignancies. Important risk factors are prolonged severe neutropenia (neutrophil count of more than 500/μL for more than 10 days), hematopoietic stem cell transplant (HSCT), and subsequent intensive chemotherapy after previous fungal infections [1–3]. One of the most common causes of invasive fungal infections is Aspergillus species [4–7]. The incidence of Aspergillus infection varies according to the underlying condition, but is most frequently observed among severely neutropenic patients. The fatality rate of invasive aspergillosis is approximately 50% to 60% [1,8].

Address correspondence to: Jeroen Jansen, Mapi Values, De Molen 84, 3995 AX Houten, The Netherlands. E-mail: Jeroen.jansen@mapivalues.com
10.1111/j.1524-4733.2006.00076.x

Amphotericin B deoxycholate and voriconazole are licensed as first-line therapy for treatment of life-threatening invasive fungal infections, including invasive aspergillosis [1,9]. Until 2002 conventional amphotericin B (CAB) was considered as the standard choice of first-line treatment in Germany. The major drawback of CAB is the poor tolerability and the severity of the toxic effects, with nephrotoxicity as the most significant adverse event. Lipid formulations of amphotericin B have significantly lower rates of nephrotoxicity, however, the hospital acquisition costs are very high. Therefore, these formulations are reserved as second-line therapy after failure or intolerance with CAB.

Voriconazole, a broad-spectrum triazole that is active against Aspergillus species, has been introduced in 2003 as an alternative to CAB. In a randomized controlled trial, first-line therapy of invasive aspergillosis with voriconazole in immunocompromised patients was compared with CAB. Voriconazole showed superior efficacy with higher response rates, better survival,

and fewer drug-related adverse events [10]. For these reasons, voriconazole is recommended as primary treatment of aspergillosis in Germany [1]. Nevertheless, CAB is still widely used mainly because of its lower drug acquisition costs.

The direct medical costs for the treatment of invasive aspergillosis are often high, and consist of the following factors: antifungal therapy costs, costs of treating adverse events, and additional costs related to hospital resources [11]. Because patients with aspergillosis are most often on medications for their underlying disease, the treatment of the invasive fungal infection results in an increased use of medical resources and costs in comparison to patients with the same underlying medical condition but without the fungal infection. Wilson and colleagues [11] estimated that the average inpatient cost related to an aspergillosis infection was about $38,000. These costs varied by underlying condition from about $31,000 among HIV patients to about $86,000 among transplant patients. Because costs of treatment of fungal infections are coupled with limited health-care resources it is of interest to perform an economic evaluation for the primary treatment of aspergillosis in Germany. In particular, we compared the current standard treatment, voriconazole, with the previous standard treatment, that is, CAB.

In Germany the former hospital financing system, which consisted partly of per-diem rates and partly of per-case rates, has been replaced by a case-mix system based on diagnosis-related groups (G-DRGs) in an attempt to improve efficiency in hospitals. For patients with an invasive aspergillosis the basic DRG reflects the underlying condition (e.g., HSCT or hematologic cancer as primary diagnosis) followed by a value for the patient clinical complexity level (PCCL) for the infection. With the introduction of the new DRG catalog of 2005 certain drugs have been granted separate reimbursement ("Zusatzentgelte") in addition to the DRG reimbursement. This regulation applies to the antifungal drugs voriconazole, lipid amphotericin B, and caspofungin. Because the treatment costs of invasive aspergillosis are expected to be high in Germany, the question that arises is whether the reimbursed costs based on the current DRG system (2005) cover the actual costs caused by invasive aspergillosis patients.

The objective of the current study is to perform an economic analysis of voriconazole as first-line treatment of invasive aspergillosis in Germany. First, a cost-effectiveness analysis is performed by which the treatment with voriconazole as first-line treatment is compared with the previous situation where CAB was used as first-line therapy. Second the costs of treatment for invasive aspergillosis from the hospital perspective are compared with the reimbursed costs based on the DRG system. Because the majority of treatment costs are the inpatient costs and the recent changes in reimbursement system reflect the inpatient situation, this comparison of costs and charges is limited to the inpatient costs.

Methods

A "lifetime" Markov model was constructed to evaluate the cost of treatment and cost-effectiveness of voriconazole in comparison to CAB in Germany. For each treatment, patients were allowed to continue on therapy, or switch to other licensed antifungal agents (OLAT) in the case of toxicity or lack of effectiveness. The 12-week Pfizer Global Comparative Aspergillosis (GCA) (307/602) study [10], a randomized controlled trial comparing voriconazole with CAB, was the primary source of data for the development of the model. Experts provided additional data and validation of the model assumptions.

Perspective

The cost-effectiveness analysis was performed from a societal perspective and a hospital perspective, as depicted in Table 1. Only direct medical costs associated with the treatment of invasive aspergillosis were included. The societal perspective included both inpatient and outpatient costs, the hospital perspective only included inpatient costs. Indirect medical costs and costs for treatment of the underlying disease were not included because the interest was in the generated

Table 1 Perspective of economic evaluations

	Societal perspective (direct costs)	Hospital perspective, costs	Hospital perspective, charges*
Analysis	Cost-effectiveness analysis that includes both inpatient and outpatient costs	• Cost-effectiveness analysis • Inpatient costs	Hospital charges: calculation of reimbursed inpatient costs based on DRG system
Calculation of inpatient costs	Real unit costs (extracted from DRG and tariffs from EBM and Gelbe Liste as a proxy for real unit costs) multiplied by health-care resource consumption	Real unit costs (extracted from DRG and tariffs from EBM and Gelbe Liste as a proxy for real unit costs) multiplied by health-care resource consumption	Charges estimated with DRG of underlying condition, length of stay and total dosage of voriconazole, caspofungin and lipid amphotericin B
Calculation of outpatient costs	Unit costs (EBM, Gelbe Liste as proxy for real unit costs) multiplied with health-care resource consumption	—	—

*German DRG 2005.
DRG, diagnosis-related group; EBM, Einheitlicher Bewertungsmaßstab.

additional costs of treating patients with aspergillosis. Indirect nonmedical costs were not included because the assumption was made that patients with aspergillosis were not employed because of the severity of the underlying disease. All costs were calculated in 2005 euros. Calculation of reimbursement of inpatient costs due to treatment of invasive aspergillosis (i.e., hospital charges) was based on the 2005 German DRG system.

Population

The model simulated a cohort of patients with proven or probable aspergillosis in patients with allogenic/autologous hematopoietic cell transplantation, acute leukemia, other hematologic cancers, solid organ transplants, AIDS/HIV, and high-dose corticosteroid recipients; the most frequent underlying medical conditions in the GCA (307/602) study. Forty percent of the modeling population was assumed neutropenic. For purposes of this analysis, we assumed the mean weight of a patient to be 70 kg (as in the clinical study) [10].

Model Structure

The model consisted of a 12-week decision tree followed by 1-week Markov cycles simulating the lifetime future course of patients (See Fig. 1).

Twelve-week decision tree. The decision tree, as described by Wenzel et al. [12], depicts the treatment pathways of voriconazole and CAB as observed in the GCA (307/602) study [10] during a 12-week follow-up. Immunocompromised patients with invasive aspergillosis enter the tree and are initially treated with either voriconazole or CAB. Patients who experience severe early toxicity (within 3 days) were consequently switched to OLAT. Patients without an early switch followed one of the following treatment pathways: continue treatment with no therapy switch; switch to other antifungal therapy due to nonresponse to first-line therapy; switch antifungal therapy due to major renal toxicity; switch antifungal therapy due to major hepatotoxicity; switch therapy due to other reasons.

Markov cycles for lifetime course. In the GCA (307/602) study treatment success was evaluated at 12 weeks follow-up. Nevertheless, the 12-week decision tree was extended with 1-week Markov cycles to simulate long-term follow-up until death to obtain an estimate of the survival times for both voriconazole and CAB. The Markov cycles consisted of the following health states: death, treatment failure, and treatment success. Patients that were dead at 12 weeks were transferred to the absorbing state "Death." Patients with a response at 12 weeks started the Markov process as a "success." Successfully treated patients at 12 weeks could only stay in the "success" state (i.e., stay alive), or experience a transition to the "death" state. Patients with a nonsuccessful response at 12 weeks who did not die entered the Markov process as a "Failure." These patients could remain a failure over the following weeks, become a success, or die.

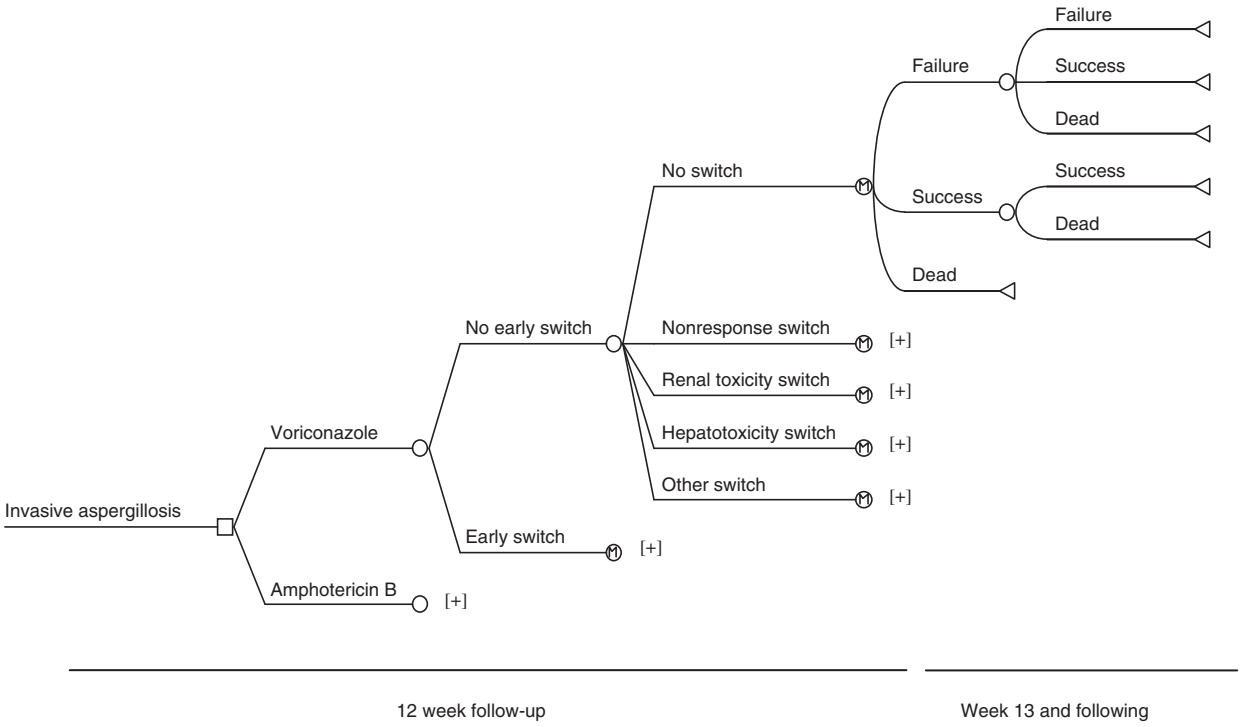

Figure 1 Decision analytic model of treatment of aspergillosis with voriconazole and conventional amphotericin B.

Assumptions of the model structure. The following assumptions and simplifications were made regarding the model structure. These were validated by the experts:

- The model assessed a single episode of invasive aspergillosis. Patients with a nonresponse, or severe toxicity only experienced a single switch to another antifungal therapy. This switch occurred within 12 weeks of treatment and only in the hospital.
- Successful treatment has been defined as either a complete or partial resolution of signs and symptoms of aspergillosis as defined in the GCA (307/602) study. For the Markov cycles the probability of successful treatment was assumed to be constant per week.
- Patients with a successful outcome experience the same survival as observed among patients with the same underlying condition that never experienced aspergillosis.
- A full course of initial therapy (including resource use) as observed in the 12 weeks of the GCA (307/602) study was assigned to all nonswitch patients independent of their outcome at 12 weeks (i.e., successes, failures, and death).
- Nonswitch patients that were a failure at week 12 and were still alive continued to receive treatment from week 13 onwards (the Markov cycles) until they died or experienced a successful outcome.
- For the switch patients a shortened course of the first-line therapy and then a full course of the second therapy was assigned to all patients independent of the outcome of the treatment at 12 weeks.
- Only switch patients that were a failure at week 12 and were still alive continued to receive treatment with the switch therapy from week 13 onwards (the Markov cycles) until they died or experienced a successful outcome.

Input Parameters

Treatment patterns. For voriconazole and CAB information on switch probabilities, proportional switch distributions, and time to switch were based on the results of the GCA (307/602) study and adapted to the local German situation by the experts. In Table 2 the switch probabilities, with the corresponding standard errors, for the treatment pathways after initiating treatment with voriconazole and CAB are presented. In Table 3 the proportional switch distributions as used in the model are presented. Step-down therapy from CAB to oral itraconazole was not considered a switch. In the model time to early switch due to severe toxicity was defined 3 days, and time to switch for other reasons was defined as 26 days for voriconazole and 16 days for CAB, based on observed results of the GCA (307/602) study.

Effectiveness. For voriconazole and CAB information on the transition probabilities for success, failure, and mortality at week 12, and corresponding standard errors, for each treatment pathway were deducted from the treatment pathway-specific success rates from the GCA (307/602) study. To obtain information on the mortality rate for each treatment pathway the ratio between the number of patients that have died among nonsuccessfully treated patients for both voriconazole followed by OLAT and CAB followed by OLAT (61.8% and 61.5%, respectively) was multiplied with the proportion of nonsuccessfully treated patients in each treatment pathway. The 12-week transition probabilities for success, failure, and mortality were the starting probabilities for the Markov process reflecting long-term follow-up.

Under the assumption that time to success and mortality were both exponentially distributed with a constant success and mortality probability per week, the transition probabilities for success, failure, and death

Table 2 Toxicity and nonresponse transition probabilities with standard error as used in the model

	Voriconazole		Conventional amphotericin B (with step-down to oral itraconazole)	
	Transition probability (SE)	Source	Transition probability (SE)	Source
Early switch	0.028 (0.01)	GCA (307/602)	0.195 (0.03)	GCA (307/602) [10]
No early switch	0.972 (0.01)	"	0.805 (0.03)	"
No switch	0.736 (0.04)	"	0.327 (0.04)	"
Nonresponse switch	0.136 (0.03)	"	0.186 (0.03)	"
Renal toxicity switch	—	"	0.383 (0.04)	"
Hepatotoxicity switch	0.029 (0.01)	"	0.029 (0.01)	"
Other switch	0.100 (0.02)	"	0.075 (0.02)	"

GCA, Global Comparative Aspergillosis.

Table 3 Proportional switch distributions

	Voriconazole (%)	Conventional amphotericin B (with step-down to oral itraconazole) (%)
Early switch		
Switch to amphotericin B	26.20	2.10
Switch to lipid amphotericin B	73.80	40.80
Switch to itraconazole	0.00	48.60
Switch to caspofungin	0.00	8.50
Switch due to nonresponse		
Switch to amphotericin B	30.60	9.40
Switch to lipid amphotericin B	32.90	15.40
Switch to itraconazole	0.00	51.30
Switch to caspofungin	36.50	23.90
Switch due to severe renal toxicity		
Switch to amphotericin B	—	0.00
Switch to lipid amphotericin B	—	29.60
Switch to itraconazole (voriconazole when on itra at begin)	—	50.40
Switch to caspofungin	—	20.00
Switch due to severe hepatotoxicity		
Switch to amphotericin B	33.00	5.7
Switch to lipid amphotericin B	15.00	24.3
Switch to itraconazole (voriconazole when on itra at begin)	0.00	40.00
Switch to caspofungin	52.00	30.00
Switch due to other reasons		
Switch to amphotericin B	8.40	7.10
Switch to lipid amphotericin B	10.00	15.70
Switch to itraconazole (voriconazole when on itra at begin)	61.30	20.00
Switch to caspofungin	20.30	57.20

per week from week 13 onwards, were deducted from the 12-week transition probabilities. In Table 4 the transition probabilities per week used to parameterize the Markov cycles to simulate the future course of failure patients at week 12 are presented. Another assumption regarding the effectiveness inputs was that successfully treated patients have the same mortality rate as observed among patients with the same underlying medical conditions who never experienced aspergillosis. The mortality probability was based on an assumed median survival of 3.5 years for the underlying conditions (about 35% 5-year survival), that is, a mortality probability per week of 0.0039 [13].

Table 4 Transition probabilities per week (with standard error)*

	Voriconazole	Conventional amphotericin B (with step-down to oral itraconazole)
Success		
Early switch	0.056 (0.02)	0.040 (0.02)
No switch	0.069 (0.02)	0.019 (0.01)
Nonresponse switch	0.025 (0.01)	0.018 (0.01)
Renal toxicity switch	0.000 (0.00)	0.040 (0.02)
Hepatotoxicity switch	0.056 (0.02)	0.040 (0.02)
Other switch	0.069 (0.02)	0.080 (0.02)
Mortality		
Early switch	0.025 (0.01)	0.039 (0.02)
No switch	0.030 (0.01)	0.055 (0.02)
Nonresponse switch	0.049 (0.02)	0.055 (0.02)
Renal toxicity switch	0.000 (0.00)	0.038 (0.02)
Hepatotoxicity switch	0.030 (0.01)	0.076 (0.02)
Other switch	0.026 (0.01)	0.022 (0.01)
Failure (=Continue treatment)		
Early switch	0.914 (0.02)	0.921 (0.02)
No switch	0.906 (0.02)	0.926 (0.02)
Nonresponse switch	0.925 (0.02)	0.927 (0.02)
Renal toxicity switch	0.000 (0.00)	0.921 (0.02)
Hepatotoxicity switch	0.914 (0.02)	0.884 (0.03)
Other switch	0.905 (0.02)	0.898 (0.03)

*Probabilities were extracted from 12-week results as reported by Herbrecht et al. [10] assuming an exponential distribution of survival and time to success.

Health-care resource consumption. Based on the results of the GCA (307/602) study as well as the experts we obtained estimates for health-care resource consumption for duration of 12 weeks. In the calculation of the average resource consumption patients that died during the first 12 weeks were taken into account. As a result differences in resource consumption for the CAB and voriconazole arm observed were partly driven by differences in mortality. The resource consumption from week 13 onwards was extrapolated from these 12-week results. For all resource consumption parameters the uncertainty reflected a range where the lowest estimate was 80% of the mean, and the highest estimate was 120% of the mean.

Antifungal therapy in the first 12 weeks. Based on the GCA (307/602) study, we assumed an average of 14 days of IV treatment and 50 days of oral treatment for all nonswitch patients on voriconazole (independent of their outcome at 12 weeks), and for nonswitch patients on CAB we assumed on average 21 days of IV treatment and 7 days of step-down therapy with itraconazole in the 12-week decision tree. For OLAT, that is, itraconazole, lipid amphotericin B, and caspofungin, the duration of therapy was derived from the experts. Itraconazole was assumed to have the same duration of IV treatment and oral treatment as voriconazole. Lipid amphotericin B and caspofungin were

assumed to have 21 days of IV treatment and 50 days step-down to oral itraconazole.

Duration of hospitalization and outpatient visits in the 12-week decision tree. Based on the GCA (307/602) study we assumed 27 days of hospital stay including 0.5 day in the intensive care unit (ICU) for nonswitch patients on voriconazole in the 12-week decision tree. For nonswitch patients on CAB we assumed 21 days of hospital stay including 0.5 day in the ICU. Patients that died during the first 12 weeks were taken into account, which explain the observed differences in length of stay between CAB and voriconazole. When patients are discharged from the hospital, antifungal treatment is continued in the outpatient setting with assumed three outpatient visits for CAB and two for other therapies. The length of stay and number of outpatient visits with voriconazole and CAB, after a switch was assumed to be the same as for a nonswitch therapy with these antifungals. Lipid amphotericin B and caspofungin were assumed to have the same length of stay and number of outpatient visits as voriconazole.

Prophylaxis, treatment, and monitoring of side effects of antifungal therapy in the 12-week decision tree. Information on prophylaxis, treatment, and monitoring of side effects of antifungal therapy was obtained from the expert panel. Paracetamol was given for the duration of IV antifungal treatment. Neutropenic patients (40% of the population) received ceftazidime, meropenem, or piperacillin-tazobactam for the duration of IV treatment in a 2 : 1 : 1 proportion. The frequency of both complete blood count and liver function testing was assumed to be twice a week during the inpatient phase of treatment. Urine analysis was performed once per week.

Screening for fungal infection in the 12-week decision tree in the 12-week model. As recommended by the expert panel, it has been assumed that ELISA was performed two times a week when the patient was in the hospital. Chest x-rays were performed once per week. Computed tomography (CT)-scans were performed two times during the inpatient phase, and bronchoalveolar lavage and a fungal culture were performed once.

Resource consumption per week used in the Markov cycles. Failure patients at week 12 continued treatment. The medical resource consumption per week from week 13 onwards for failure patients was calculated as follows. Individual data on hospital stay up to week 12 from the GCA (307/602) study were extrapolated after week 12 by fitting an exponential distribution, and it was observed that the weekly transition probability of hospital discharge was comparable to the weekly transition probability of failure to success. In addition, at week 12 about 50% of the failure patients remained hospitalized. Combining these two probabilities was the basis for estimating that from week 13 onwards 50% of the failure patients each week are treated in the hospital with the antifungal therapy (including treatment of side effects and screening) administered at week 12. The remaining 50% are treated in an outpatient setting and continued with oral antifungal treatment administered at week 12.

Unit Costs

The costs per unit of medical resource consumption are presented in euros (2005) for the societal perspective and hospital perspective in Table 5.

The unit costs related to stay and nursing were extracted from detailed information from the G-DRG provided by the Institut für das Entgeltsystem im Krankenhaus (InEk) [14]. Rational for usage of these data is that German DRGs are based on real cost calculation and provide a solid estimate to address resource (e.g., nursing requirements) use for specific indications. DRGs related to treatment of the frequent underlying conditions of invasive aspergillosis were identified. The DRG data do not explicitly reflect the true costs of aspergillosis therapy. But according to the advice provided by the clinical experts, resource use of the identified "proxy DRGs" represent a good estimate for real costs of aspergillosis therapy based on a large sample of patients from the DRG database. From the identified DRGs it was determined which DRGs best reflect the treatment of invasive aspergillosis in terms of nursing intensity and hospital department, and for which the vast majority of costs (more than 80%) were driven by normal care, in contrast to intensive care. The basic costs and costs of normal care, excluding drug costs and medical device costs, in combination with the length of stay corresponding to the DRGs were used to calculate an average hospital cost per day for normal care. To obtain these unit costs for intensive care two DRGs were chosen with comparable costs related to normal care but different costs related to intensive care. The difference in basic and intensive care costs, excluding drug costs and medical device costs, were divided by the difference in corresponding length of stay to obtain the unit hospital costs. Other unit cost of medical resource consumption was obtained from the Einheitlicher Bewertungsmaßstab (EBM) [15], used as a proxy for real costs, and Gelbe Liste for drugs [16].

Analysis

Calculation of costs in 12-week decision tree. Similar to Wenzel et al. [12] the treatment costs as used in the 12-week decision tree were calculated as follows:

The "cost of a full course of first-line treatment without a switch" included costs for antifungal ther-

Table 5 Description costs from limited societal perspective and hospital perspective

	Details	Cost per day or cost per unit (€)	Source
Antifungal therapy			
Conventional amphotericin B	1 mg/kg/day IV	118.65	Gelbe Liste Pharmindex/clinical expert [16]
AmBisome (lipid amphotericin B)	3 mg/kg/day IV	821.91	"
Itraconazole	400 mg oral/day	17.304	"
	400 mg/day IV	305.616	"
	600 mg/day IV	458.424	"
Caspofungin	70 mg/day/kg IV	779.42	"
	50 mg/day/kg IV	614.78	"
Voriconazole	2 × 200 mg oral/day	116.61	"
	8 mg/kg/day IV	579.52	"
	12 mg/kg/day IV	869.27	"
Prophylaxis and treatment of side effects of antifungal therapy			"
Paracetamol	1 g/day IV	0.13	"
Ceftazidime	5 g/day oral	119.2	"
Meropenem	60 mg/kg/day IV	181.6	"
Pethidine	25 mg/day IV	0.83	"
Hydrocortisone	25 mg/day IV	0.5387	"
Piperacillin/Tazobactam	4 g/0.5 g tds	33.98	"
Monitoring for side effects			
Complete blood count		5.83	EBM Einheitlicher Bewertungsmaßstab [15]
Urinalysis	Nonautomated, with microscopy	5.48	"
Liver function test		11.63	"
Screening for fungal infection			
Galactomannan assay	ELISA	21.63	"
Chest x-ray		52.03	"
CT scan		294.12	"
Bronchoalveolar lavage		150.12	"
Fungal culture	Nonblood	9.83	"
Hospitalization/outpatient care			
Intensive care unit per diem		1010	Extracted from G-DRG 2005 [14]
Inpatient per diem		200	"
Outpatient specialist visit		33.11	EBM Einheitlicher Bewertungsmaßstab [15]

CT, computed tomography; tds, total dissolved solids.

apy, diagnosis, monitoring, and treatment of side effects, screening for fungal infections, hospitalization, and outpatient care. In addition, the "mean daily hospital costs" were calculated.

The "cost of a full course of switch therapy" also included cost for antifungal therapy, diagnosis, monitoring and treatment of side effects, screening for fungal infections, hospitalization, and outpatient care.

With the decision tree the "costs for each type of switch" (i.e., early switch, nonresponse switch, etc.) were calculated by adding the weighted mean "costs of a full course of switch therapy" using the proportional switch distribution in Table 3 to the "costs of first-line treatment up to the switch." The "costs of first-line treatment up to the switch" were calculated by multiplying the "mean daily hospital costs" by the number of days on first-line therapy until the switch.

To obtain the "total costs for each treatment arm" (i.e., voriconazole, CAB, and itraconazole) the "costs for each type of switch" were weighted using the switch proportions in Table 2.

Calculation of costs in the Markov cycles. For each antifungal therapy administered at week 12 the "Cost of course of treatment per week" was determined by calculating the average of the "weekly hospital cost" and "weekly outpatient treatment costs." It was assumed that per week 50% of the patients were treated on an inpatient basis, and the other on an outpatient basis. For each type of switch the "total treatment costs per week" were calculated by the weighed mean of the "cost of course of treatment per week" using the proportional switch distributions (Table 3).

Calculation of reimbursed hospital costs based on G-DRG system. Hospital charges for the invasive aspergillosis infections based on the G-DRG 2005 were estimated as follows: The additional length of stay in hospital due to an aspergillosis infection was estimated from the model. From the DRGs corresponding to hematologic cancer, stem cell transplants (autogen and allogen), and HIV, the length of stay due to these underlying conditions was obtained as well as average reimbursed costs, that is, the charges for patients only suffering from the underlying condition. The sum of the additional length of stay resulting from the infection and the length of stay associated with the underlying condition was used to calculate the total length of stay. This total length of stay was used to determine the reimbursed cost for patients with the infection and underlying disease using G-DRG 2005. The difference between these charges, for the reimbursement of costs related to the underlying condition with an infection, and the average charges of the

underlying condition were assumed the charges for the aspergillosis infection because of additional length of stay.

For patients treated with voriconazole, caspofungin or lipid amphotericin B additional money is available based on the total prescribed dosage. With the model this total prescribed dosage was estimated for each of these drugs for both the voriconazole arm and CAB arm.

The total hospital charges for treatment of invasive aspergillosis equal the sum of charges due to additional length of stay and additional charges of prescription of voriconazole, caspofungin, or lipid amphotericin B. Based on the distribution of underlying conditions as observed in the GCA (307/602) study a weighted average of hospital charges per treatment arm was calculated. In both arms the distribution of underlying condition was assumed as follows: 28% allogeneic stem cell transplants, 7% autologous stem cell transplants, 45% acute leukemia, 15% other hematologic cancer, and 5% AIDS.

Cost-effectiveness analysis. The cost-effectiveness analysis was performed for total costs of both inpatient and outpatient cost from the societal perspective and the hospital perspective (inpatient costs). Both the costs and effectiveness point estimates were presented along with the uncertainty distribution of these means reflected by the 2.5th percentile (p2.5) and 97.5th percentile (p97.5). For the cost-effectiveness parameters the distribution of incremental costs and effectiveness as well as acceptability curves are presented. The uncertainty, as expressed by p2.5 and p97.5, and by acceptability curves of the cost-effectiveness parameters were estimated by means of 2nd order Monte Carlo simulation. From distributions reflecting the uncertainty of the input parameters a random value was sampled, plugged in the model, and the corresponding costs and effectiveness were calculated with the model. This was repeated 1000 times to obtain distributions of the outcomes. The point estimate and the uncertainty of the input parameters (e.g., the standard errors for the efficacy input parameters obtained from trial, and assumed uncertainty of 20% for the resource consumption parameters) were described by gamma and beta distributions. In the base-case scenario no discounting of costs or effects was applied. In additional analysis discount rates of 3% and 5% were applied on both costs and effects.

Results

Effects

Patients starting on voriconazole had a 52.9% (48.2%; 58.1%) chance of a successful outcome at 12 weeks, which was higher than those starting on CAB with 32.6% (28.2%; 37.8%). The 12-week survival of 70.9% (65.9%; 75.6%) for treatment of invasive aspergillosis with voriconazole corresponded to a mean survival of 174.4 (159.4; 191.3) life-weeks. Treatment initiated with CAB resulted in a 12-week survival of 58.6% (52.8; 63.5) and corresponded to a mean survival of 119.4 (105.8; 132.5) life-weeks.

Costs

In Table 6 the treatment costs after 12 weeks and total treatment costs are presented. The mean total treatment costs (from lifelong model) for treatment initiated with voriconazole were about €30,000 and when CAB would have been used as first-line therapy the costs were about €27,000. Standardization by survival resulted in costs of €172 per life-week for the voriconazole arm, and €222 per life-week for the CAB arm. The mean inpatient costs (hospital perspective from lifelong model) for treatment initiated with voriconazole or CAB were about €26,000. The corresponding costs per life-week were €151 for the voriconazole arm, and €218 for the CAB arm.

Incremental Cost-Effectiveness

Table 7 shows the cost-effectiveness of voriconazole in comparison to CAB in terms of 12-week success and survival in life-weeks. From the societal perspective the larger treatment costs at 12 weeks in combination with a 20%-point effectiveness advantage for voriconazole resulted in an incremental cost-effectiveness ratio of about €25,000 for each additional successfully treated patient. The incremental costs per life-week gained with voriconazole in comparison to CAB were €62.34 (and corresponds to €3242 per life-year gained). From the hospital perspective the incremental costs at 12 weeks for each additional successfully treated

Table 6 Treatment costs from societal perspective and hospital perspective

	Voriconazole mean (€) (p2.5; p97.5)	Conventional amphotericin B Mean (€) (p2.5; p97.5)
Societal perspective		
12-week total cost	25,353 (18,550; 32,109)	20,092 (15,648; 25,297)
Total costs from lifelong model	30,026 (23,118; 37,947)	26,596 (21,259; 34,263)
Total costs per life-week from lifelong model	172 (133; 220)	222 (173; 288)
Hospital perspective		
12-week inpatient costs	22,090 (16,395; 27,507)	19,637 (15,218; 25,177)
Inpatient costs from lifelong model	26,440 (20,489; 32,864)	26,058 (20,622; 34,152)
Total inpatient costs per life-week from lifelong model	151 (116; 192)	218 (171; 291)

p2.5 and p97.5, indicate 2.5th and 97.5 percentile of the uncertainty distribution, respectively.

Table 7 Incremental costs and incremental effectiveness, ICER, and cost-effectiveness of voriconazole versus conventional amphotericin B

	Incremental costs (€) mean (p2.5; p97.5)	Incremental effectiveness mean (p2.5; p97.5)	ICER (€) mean
Total treatment costs (societal perspective)			
12-week horizon	5260 (–3905; 13,791)	0.20 (0.13; 0.27)%*	25,195 per successful patient
Lifetime horizon	3430 (–7452; 13,414)	55.0 (36.6; 74.6) weeks	62.34 per life-week gained
Inpatient costs (hospital perspective)			
12-week horizon	2453 (–5369; 9728)	0.20 (0.13; 0.27)%*	12,084 per successful patient
Lifetime horizon	328 (–9308; 8921)	55.0 (36.6; 74.6) weeks	6.95 per life-week gained

*Incremental effectiveness expressed as percentage-points of additional successful patients.
ICER, incremental cost-effectiveness ratio; p2.5 and p97.5, indicate 2.5th and 97.5 percentile of the uncertainty distribution, respectively.

patient were about €12,000. The incremental costs per life-week gained with voriconazole were €6.95 (and corresponds to €361 per life-year gained). From the limited societal perspective the probability that voriconazole is cost-effective in comparison to CAB given a willingness to pay of about €200 for each life-week gained (corresponds to €11,000 per life-year) is about 90% (See Fig. 2). From the hospital perspective voriconazole is expected to be cost-effective for a willingness to pay of about €100 for each life-week gained.

When discount rates of 3% and 5% per year were applied to both costs and effects the incremental effectiveness reduced to 49.0 and 45.7 weeks, respectively, the corresponding incremental total costs from the societal perspective were €3431 and €3432. The incremental costs per life-week gained with voriconazole in comparison to CAB were €70.03 and €75.03, respectively.

Hospital Charges Based on G-DRG System

The hospital charges with the DRG system are defined by the total dosage of voriconazole, caspofungin, or lipid amphotericin B, and the underlying condition in combination with the length of stay (For CAB no additional reimbursement "Zusatzentgelt" is granted within the DRG system.

For the voriconazole arm the total average inpatient dosage for voriconazole IV was 9.03 g (6.38; 11.63), the inpatient dosage of oral voriconazole was 5.78 g (4.27; 7.60). The total average inpatient dosage of caspofungin and lipid amphotericin B are 0.12 g (0.09; 0.17) and 0.47 g (0.31; 0.69), respectively. The corresponding reimbursed costs due to the use of these drugs for a patient initially treated with voriconazole are €9369 (5376; 11,829). For the CAB arm the total average inpatient dosage of caspofungin and lipid amphotericin B were 0.22 g (0.17; 0.30) and 1.26 g (0.95; 1.67), respectively. The corresponding charged costs due to the use of these drugs for a patient initially treated with CAB are €5747 (4682; 7874).

According to the model the mean length of stay for a patient treated with voriconazole was 39.9 days (30.5; 49.9) and with CAB 45.5 days (36.1; 59.4). In Table 8 the total charged costs available for the treatment of aspergillosis infection (based on dosage and length of stay) are presented stratified by different DRGs for the underlying conditions. Based on the underlying condition, the total charged costs vary from

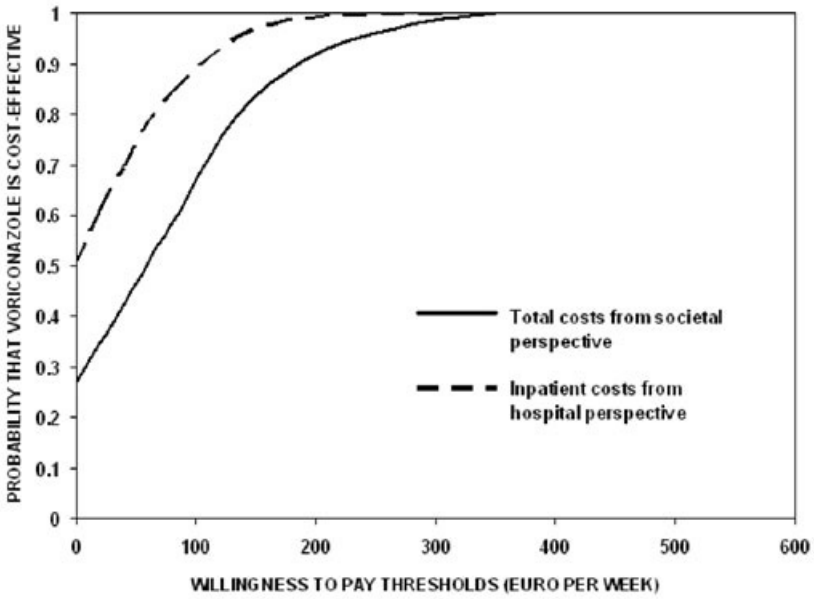

Figure 2 Acceptability curve of voriconazole versus conventional amphotericin B as measured in life-weeks gained from the societal and hospital perspectives.

Table 8 Hospital charges based on German DRG 2005 by treatment arm and underlying condition

			Voriconazole			Amphotericin B		
	G-DRG codes [14]	Percentage of patients in model assumed (%)	Charges based on LOS	Charges of total dosage of voriconazole, caspofungin, or lipid amphotericin B	Total charges (p2.5; p97.5)	Charges based on LOS	Charges of total dosage of voriconazole, caspofungin, or lipid amphotericin B	Total charges (p2.5; p97.5)
Acute leukemia	R60A-R60E R63A-R63E	45	13,996	9369	23,365 (18.052; 29,040)	17,184	5747	22,931 (17,601; 30,770)
Other hematologic cancer	R01A R01B R02Z R03Z R04A R04B R05Z R06Z R07Z R08Z R09Z R10Z R11A-R15Z R61A-R62C	15	9,662	9369	19,030 (15,608; 22,685)	11,715	5747	17,462 (14,029; 22,511)
Allogeneic stem cell transplants	A04A-A04E	28	35,422	9369	44,791 (30,343; 60,222)	44,090	5747	49,837 (35,343 71,155)
Autologous stem cell transplants	A15A-A15D	7	29,572	9369	38,940 (29,113; 49,437)	35,468	5747	41,215 (31,356; 55,715)
AIDS	S62Z-S65Z	5	12,662	9369	19,597 (15,933 23,510)	15,356	5747	18,173 (14,497; 23,579)
Total		100	20,337	9369	29,616 (21,795 37,969)	25,048	5747	30,686 (22,841; 42.226)

G-DRG, German diagnosis-related group; LOS, length of stay.

€19,030 (15,608; 22,685) (average from DRGs for other hematologic cancer) to €44,791 (30,343; 60,222) (allogenic stem cell transplants) for treatment initiated with voriconazole and from €17,462 (14,029; 22,511) (average from DRGs for other hematologic cancer) to €49,837 (35,343; 71,155) (allogenic stem cell transplants) for treatment initiated with CAB. The weighted average of charged costs based on the distribution of underlying conditions according to the GCA (307/602) study was €29,616 (21,795; 37,969) for the voriconazole arm and €30,686 (22,841; 42,226) for the CAB arm.

Discussion

In the present study the cost and cost-effectiveness of voriconazole as first-line treatment of invasive aspergillosis in Germany was evaluated. According to our modeling, the short-term advantage of first-line treatment with voriconazole in terms of successfully treated patients as observed in the clinical trial [10] was maintained in the long term. The model showed a mean survival that is about 58 weeks longer than the survival expected when CAB would have been the first-line choice of treatment for invasive aspergillosis. In addition, voriconazole is also a more cost-effective first-line treatment than CAB. The higher total treatment cost with voriconazole is acceptable given the higher effectiveness. The incremental costs per life-week gained with voriconazole in comparison to CAB was €62, that is, €3224 per life-year gained, well below an assumed willingness to pay threshold in Germany. Voriconazole is more effective, more cost-effective, and indicated as first-line treatment of invasive aspergillosis over CAB.

The second research question of this study was whether the real costs of this favorable treatment are fully reimbursed, especially given the recent change in the reimbursement system in Germany effective since beginning of 2005. Because the majority of treatment costs are the inpatient costs and the recent changes in reimbursement system reflect the inpatient situation, this evaluation was limited to the inpatient costs. The real inpatient costs (i.e., hospital perspective) for treatment of invasive aspergillosis as estimated with the model were about €26,000 for both voriconazole and CAB. Invasive aspergillosis is a complication of several different underlying diseases represented in different DRGs. The charges related to an aspergillosis infection are defined by the underlying condition, which defines the DRG, in combination with the length of stay, complexity level, and the total dosage of voriconazole, caspofungin, or lipid amphotericin B prescribed. Based on the length of stay and total inpatient dosage of these drugs suggested by the model, the expected hospital charges for aspergillosis for different DRGs were calculated. These costs varied depending on the underlying condition between about €19,000 and €45,000 for the voriconazole arm. (For the CAB arm comparable figures were observed; see Table 8). Based on the assumed distribution of underlying conditions, and thereby the used DRGs, the average charges, and therefore the reimbursed costs, were about €30,000. Hence, on the average the inpatient costs for treatment

of an invasive aspergillosis infection are expected to be reimbursed by the G-DRG 2005 system. Because the model estimates the average inpatient costs (from the hospital perspective) per patient for a cohort of patients with different underlying conditions it provides only limited information when the average inpatients costs are compared with the charges per DRG code for each of the underlying conditions; for an appropriate comparison subgroup analysis by underlying condition should be performed. Anyhow, the distribution of underlying conditions as used in the present study shows that the charges cover costs.

Prospective budgeting according to the DRG system gives strong economic incentives to hospitals but also bares considerable risks for hospitals when treating severe, resource-intensive, and costly indications. Adequate reimbursement for these indications ensures that hospitals take the risk of continuously investing in, for example, specialized transplant units to deliver adequate and high-level care for severely diseased patients. For high-level-care hospitals/specialized hospital units this can only be achieved if frequently occurring complications like aspergillosis are adequately represented in the DRG system.

Model issues

To develop a decision analytic model for the treatment of invasive aspergillosis the practice of invasive aspergillosis was simplified, and several assumptions were made with respect to the structure of the model. Treatment patterns were reflected with a decision tree. According to the experts treatment switches occur in the first 12 weeks of treatment, and therefore it was valid that the structure of the model was not able to capture treatment switches after week 12.

In the 12-week GCA (307/602) study an average of 0.51 switches in the voriconazole arm and 1.35 in the CAB arm were observed. Alternatively, 13% of voriconazole patients and 40% of CAB patients had two or more switches to OLATs [17]. By structure the decision tree allows for one switch in treatment. In the model multiple switches are captured by the proportional switch distributions, which are a reflection of days on a particular OLAT. A consequence of this approach is that the inpatient length of treatment and therefore various resource utilizations are underestimated. With one treatment switch in the model the total length of stay among switch patients equals time to switch plus the length of stay post treatment switch according to the proportional switch distributions and the weighted average of one OLAT length of treatment. The approach does not include the time to switch from the first to the second switch for example. Hence, the model probably underestimates the total costs for patients with multiple switches, with probably a larger underestimation for the CAB arm as according to the GCA (307/602) study more OLATs have been used in this therapy arm compared with the voriconazole arm.

The 12-week results as observed in the GCA (307/602) study were extrapolated into a lifelong model by which survival time could be estimated. We assumed that the weekly probabilities that reflect a "transition" from failure to success or death, or a "transition" from success to death beyond week 12 were constant over time. Hence, the probability density function (PDF) of survival time given success or failure, and the PDF of success are described by an exponential distribution. As far as we know the literature does not provide information that invalidates or supports this assumption of an exponential distribution. Nevertheless, because the majority of transitions from failure to success or death have occurred before week 12, the type of distribution reflecting the development of transition probabilities from failure to success or death over time beyond week 12 has only limited impact on the results. The majority of transitions after week 12 reflect dying from the underlying condition, and given the lack of information regarding long-term distributions of survival time, we assumed an exponential distribution for survival in accordance with the opinion of the expert panel.

For switch patients the extracted success, failure, and mortality probability per week for a given treatment pathway based on the 12-week results may have resulted in an underestimation of survival times. For these patients, the weekly success probability of the OLAT is higher than the first-line therapy, either because of a more potent drug or because of the fact that the drug is better tolerated. Hence, for a proper extrapolation the results of the OLAT for treatment pathway should be used. Unfortunately, this information was not available. Patients initially on CAB experience the most treatments switches, and by using the combined results of first-line treatment and OLAT the underestimation of the long-term survival among these patients is expected to be the largest. Hence, the incremental survival of voriconazole in comparison to CAB might be overestimated.

No difference was made in the medical resource consumption for successes and failures by type of treatment switch as a result of the fact that: 1) estimates on medical resource consumption for all the different subgroups from the GCA (307/602) study were characterized by large uncertainty, and 2) therefore, it was impossible to obtain reliable information on resource consumption for both success and failures among the different subgroups from the experts. The use of aggregate level information independent of the outcome at 12 weeks has probably resulted in an overestimation of resource consumption and costs for voriconazole in comparison to CAB because a higher proportion of successes were observed in the voriconazole arm and it is expected that successes are

observed earlier with voriconazole than successes with CAB.

In conclusion, the first-line treatment of invasive aspergillosis with voriconazole in Germany is a cost-effective choice. From the hospital perspective the inpatient costs for voriconazole and CAB are comparable, and are expected to be reimbursed based on the German DRG system 2005. Hence, economic arguments do not interfere with the German guidelines that state that voriconazole is first choice of treatment of invasive aspergillosis [1].

The following individuals were members of the expert committee that validated the model assumptions and input: Prof Dr M Ruhnke, Department of Medicine, Division Onkology/Hematology, Charite Universitätsmedizin Berlin, Campus Charite Mitte, Berlin; Dr S Schwartz Med. Klinik III, Charite—Universitätsmedizin Berlin, Campus Benjamin Franklin, Freie Universität; Prof Dr M Karthaus, Department of Internal Medicine, Medical Clinic II, Ev. Johannes-Krankenhaus, Bielefeld; Dr AJ Ullmann, III, Medical Klinik u. Poliklinik, Johannes Gutenberg-Universität, Mainz, Germany; Dr OA Cornely, Klinikum der Universität, Koeln; Prof Dr WK Kern, Innere Medical II/Infektiologie, Medical Universitätsklinik, Freiburg, Germany. Dr Craig Roberts and Dr Dietmar Pfründer provided valuable comments to the article.

Source of financial support: This study was funded by Pfizer.

Acknowledgments

Dr. Stefan Schwartz, Department of Internal Medicine III, Charité Campus Benjamin Franklin, Berlin, Germany helped validating the model assumptions and input. Dr. Craig Roberts, Pfizer Inc., New York, USA and Dr. Dietmar Pfruender, Pfizer Pharma GmbH, Karlsruhe, Germany provided valuable comments to the manuscript.

References

1 Bohme A, Ruhnke M, Buchheidt D, et al. Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Treatment of fungal infections in hematology and oncology—guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003;82(Suppl. 2):S133–40.

2 Ruhnke M, Bohme A, Buchheidt D, et al. Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Diagnosis of invasive fungal infections in hematology and oncology—guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003;82(Suppl. 2):S141–8.

3 Denning DW. Invasive aspergillosis. Clin Infect Dis 1998;26:781–803.

4 Dixon DM, McNeil MM, Cohen ML, et al. Fungal infections: a growing threat. Public Health Rep 1996;111:226–35.

5 Lamagni TL, Evans BG, Shigematsu M, Johnson EM. Emerging trends in the epidemiology of invasive mycoses in England and Wales (1990–9). Epidemiol Infect 2001;126:397–414.

6 Groll AH, Shah PM, Mentzel C, et al. Trends in the postmortem epidemiology of invasive fungal infections at a University hospital. J Infect 1996;33:23–32.

7 Groll AH, Ritter J, Muller FM. [Prevention of fungal infections in children and adolescents with cancer]. Klin Padiatr 2001;213(Suppl. 1):S50–68.

8 Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001;32:358–66.

9 Dismukes WE. Introduction to antifungal drugs. Clin Infect Dis 2000;30:653–7.

10 Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–15.

11 Wilson LS, Reyes CM, Stolpman M, et al. The direct costs and incidence of systemic fungal infections. Value Health 2002;5:26–34.

12 Wenzel R, Del Favero A, Kibbler C, et al. Economic evaluation of voriconazole compared with conventional amphotericin B for the primary treatment of aspergillosis in immunocompromised patients. J Antimicrob Chemother 2005;55:352–61.

13 Coleman MP, Gatta G, Verdecchia A, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 2003;14(Suppl. 5):S128–49.

14 G-DRG-Fallpauschalen-Katalog 2005. Available from G-DRG via: http://www.g-drg.de [Accessed August 30, 2005].

15 Einheitlicher Bewertungsmaßstab (EBM). Available from online-EBM via: http://www.e-bis.de [Accessed August 30, 2005].

16 Gelbe Liste Pharmindex. Available from Medizinische Medien Informations GmbH via: http://www.gelbeliste.de [Accessed May 2004].

17 Lewis JS, Boucher HW, Lubowski TJ, et al. Cost advantage of voriconazole over amphotericin B deoxycholate for the primary treatment of invasive aspergillosis. Pharmacotherapy 2005;25:839–46.